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Correlation between pharmacokinetic/pharmacodynamic indices and clinical outcomes in Japanese patients with skin and soft tissue infections treated with daptomycin: analysis of a phase III study☆

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ABSTRACT

The relationships between pharmacokinetic (PK)/pharmacodynamic (PD) indices and outcomes were investigated in patients with skin and soft tissue infection (SSTI) who received daptomycin at 4 mg/kg/day. Efficacy was evaluated in 55 patients from whom *Staphylococcus aureus* was isolated, with success rates of 94.5% and 69.1% for clinical and microbiological responses, respectively. The odds ratio for the relationship between the area under the day 1 concentration–time curve ($AUC_{0-24\ h}$) to the MIC and the probability of clinical success was 1.03 (95% confidence interval [CI] 0.73–1.45), and that for the relationship for probability of microbiological success was 0.94 (95% CI 0.81–1.09). In 82 patients in the safety analysis, only 1 met the creatine phosphokinase (CPK) elevation criteria, and this patient's minimum concentration (C_{min}) of plasma daptomycin was 5.37 μg/mL. No significant relationship was found between peak CPK and C_{min} (Pearson's correlation coefficient −0.0452). In conclusion, no clear correlation between PK/PD indices and the probability of efficacy or safety events was demonstrated when daptomycin was administered in SSTI patients using the clinically recommended dosage of 4 mg/kg/day.

1. Introduction

Daptomycin (Cubicin®) is a cyclic lipopeptide antibiotic that is approved for the treatment of skin and soft tissue infections (SSTIs) caused by gram-positive cocci and of bacteremia caused by *Staphylococcus aureus*. Several reports of pharmacokinetic (PK)/pharmacodynamic (PD) analyses of daptomycin based on an in vivo infection model described the ratio of area under the plasma concentration–time curve to the MIC ($AUC_{0-24\ h}$/MIC) as the PK/PD index associated with efficacy (Louie et al., 2001; Safdar et al., 2004). However, the magnitude of $AUC_{0-24\ h}$/MIC associated with efficacy based on data from clinical studies has not been described.

The relationship between daptomycin exposure and creatine phosphokinase (CPK) elevation has been reported previously, based on data from patients who received daptomycin at 6 mg/kg/day for the treatment of bacteremia or endocarditis (Bhavnani et al., 2010). The evaluation of the proposed cut-off points to adverse events, however, has not been performed in patients receiving daptomycin at 4 mg/kg/day for the treatment of SSTIs. The clinical outcomes of a phase III study in patients with SSTIs caused by methicillin-resistant *S. aureus* (MRSA) or other gram-positive cocci treated with daptomycin have been reported by Aikawa et al. (2013). Using data from a subpopulation of that study, we investigated the relationships between daptomycin exposure and clinical outcomes in patients with SSTIs who received daptomycin at 4 mg/kg/day.

2. Materials and methods

2.1. Study design and population for analysis

We analyzed data from a subset population of a phase III study of daptomycin in Japanese patients with SSTI caused by gram-positive cocci conducted between 2008 and 2010 (Aikawa et al., 2013). The study was reviewed and approved by the ethics committee of each institution, and written informed consent was obtained from the patients before enrollment. This study is registered at ClinicalTrials.gov

☆ Clinical trial registration: ClinicalTrials.gov, NCT00770341.

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(NCT00770341). Inclusion criteria for the phase III study were 1) isolation of MRSA from specimens obtained within 3 days before starting treatment or the detection of gram-positive cocci and a suspicion of MRSA infection and 2) presence of at least 3 of the following: drainage/exudate, erythema, fluctuance, localized warmth, pain/tenderness, swelling/induration, temperature >37.5 °C (oral) or 37 °C (armpit), white blood cell count outside the normal range, stab cells >15%, pulse rate >90/min, respiratory rate >20/min, and positive C-reactive protein.

In this study, patients were treated with 4 mg/kg/day intravenous daptomycin over 30 min for 7–14 days. CPK was measured twice a week in the treatment period. The population for each analysis was defined as follows: PK/PD analysis population for safety: patients who received at least 1 dose of daptomycin and at least 1 blood sample for plasma concentration measurement; PK/PD analysis population for efficacy: patients who 1) were included in the PK/PD analysis population for safety, 2) received at least 4 days of treatment, 3) had clinical or microbiological assessment data at test of cure (TOC), 4) did not receive any prohibited concomitant antibiotics, 5) did not have important deviations from the protocol, and 6) were infected with *S. aureus* (methicillin sensitive or resistant). The MIC of daptomycin against *S. aureus* at baseline was measured by microdilution methods in accordance with the Clinical and Laboratory Standards Institute (CLSI) testing guidelines (M7-A7, 2006).

2.2. PK sampling and measurement of plasma level

Daptomycin was intravenously infused over 30 min, and blood samples were collected at the following 5 time points: prior to and at the end of infusion, 30 min to 2 h, and 4–10 h postadministration on day 4 and prior to infusion on day 5. Blood was collected in Na–heparin tubes and stored on ice immediately. Plasma was obtained by centrifugation at approximately 3000–4000 rpm for 15 minutes within 2 h of blood collection. The plasma (1.5 mL) was then transferred to a polypropylene tube, which was stored frozen at −20 °C. The daptomycin concentration was measured at PPD® (Richmond, Virginia, USA). A 300-μL aliquot was used for reverse-phase high-performance liquid chromatography (Waters WISP 717 plus) with ultraviolet absorbance detection. The minimum quantifiable level was 3.0 μg/mL. The daptomycin standard for quantification was provided by Cubist Pharmaceuticals (Lexington, MA, USA).

2.3. Population PK modeling

Our analysis included the data from 545 subjects who were enrolled in phase I and phase III studies conducted in Japan (127 subjects), which were reported by Dvorchik et al. (2004) (282 subjects), or who were enrolled in 3 other phase I and phase III studies in non-Japanese (136 subjects). A total of 5586 daptomycin samples for PK (1255 from Japanese and 4331 from non-Japanese) were included in the data set. Doses ranged from 2 to 12 mg/kg among the studies described by Dvorchik et al. (2004) and among the additional 20 studies evaluated. Plasma concentration data for daptomycin were analyzed using nonlinear mixed-effects modeling (NONMEM, version 6). The first-order conditional estimation with interaction method was used for all analyses. Our population PK model was further developed in reference to the published model (Dvorchik et al., 2004). We investigated the influence of the covariates reported by Dvorchik et al. (2004), namely, gender, body weight, temperature, infection status, disease diagnosis, dialysis and dialysis membrane type, creatinine clearance, and ethnicity, on daptomycin PK. In addition, a new covariate representing origin, Japan versus other countries, was also examined.

The final population PK model was used to generate the empirical Bayesian PK parameter estimates. The individual day 1 AUCs were calculated based on simulated daptomycin concentrations. Steady-state exposures were estimated using the individual empirical Bayes parameters. Estimated daptomycin exposure and PK parameters included minimum concentration (C_{min}), $AUC_{0-24\ h}$, weight-adjusted steady-state volume of distribution (Vss), weight-adjusted clearance (CL), and half-life ($t_{1/2}$). The predictability of the model was evaluated using a visual predictive check. One thousand data sets were simulated for daptomycin concentrations based on the final model. The observed and simulated data sets in a steady state were each divided into bins of approximately equal numbers of observations by ranges of time after dose and then stratified by dose (4 and 6 mg/kg). For each separate bin in the observed and simulated data, the 5th, 50th, and 95th percentiles were calculated. The observed data were compared to the 5th, 50th, and 95th percentiles of the observed and simulated data.

2.4. PD endpoints

Clinical and microbiological responses were evaluated at TOC. Clinical success was defined as resolution or partial resolution of signs and symptoms of SSTI in patients who did not receive additional antimicrobial agents that could potentially have been effective against the causative pathogen during the study period. Microbiological success was defined as "eradication" (admission pathogen absent in culture) or "presumed eradication" (no material available for culture due to the infection site being cured or improved). The Independent External Adjudication Committee (IEAC), consisting of 5 medical experts blinded to study therapy, reviewed and determined the final assessment of efficacy.

CPK elevation represented the safety endpoint of interest, with the upper limit of normal (ULN) for CPK concentration being defined as 200 U/L. Patients with CPK concentrations meeting either of the following conditions were classified as having elevated CPK: 1) no CPK elevation at baseline followed by CPK elevations ≥3 × ULN based on 2 sequential measurements during the period from day 4 to 2 days after the end of therapy, with 1 of 2 CPK elevations ≥5 × ULN or 2) baseline CPK greater than the ULN followed by CPK elevation ≥5 × ULN based on 2 sequential measurements during the period from day 4 to 3 days after the end of therapy (Bhavnani et al., 2010).

2.5. PK/PD analyses

Summary statistics including the geometric mean (GM) and corresponding 95% confidence intervals (CIs), minimum, median, and maximum were provided for PK parameters. Clinical and microbiological responses were summarized by exposure grouped by quartiles. The relationship between response and exposure grouped in this manner was assessed using Mantel–Haenszel chi-square test. In addition, logistic regression models with day 1 and steady-state $AUC_{0-24\ h}$ and $AUC_{0-24\ h}$/MIC evaluated as continuous covariates were used to investigate the effect of exposure on the clinical and microbiological responses. Similarly, the relationship between CPK elevation and C_{min} grouped by quartiles and as a continuous covariate was evaluated. Pearson's correlation coefficient was calculated for the relationship between C_{min} and peak CPK. SAS version 9.3 for Windows (SAS, Cary, NC, USA) was used to perform all analyses. All statistical tests were conducted at the 0.05 significance level (2 sided).

3. Results

3.1. Patient population and daptomycin susceptibility for S. aureus

A total of 82 patients were included in the PK/PD analysis population for safety, and 55 patients were included in the PK/PD analysis population for efficacy. The patient characteristics for the PK/PD analysis populations for safety and efficacy are shown in Table 1. The distribution of daptomycin susceptibility for *S. aureus* stratified by methicillin-resistant and methicillin-susceptible isolates is shown in Table 2. All isolates were found to be susceptible to daptomycin according to the CLSI criterion (1 μg/mL).

Table 1
Baseline demographics in patients who were included in the PK/PD analyses of safety and efficacy.

Baseline demographics	PK/PD analysis population for safety (n = 82)	PK/PD analysis population for efficacy (n = 55)
Median age (range) [years]	70 (22–92)	70 (28–92)
Sex male (%)	44 (53.7)	31 (56.4)
Median body weight (range) [kg]	54.0 (29.6–117.8)	53.5 (31.2–108.0)
Median creatinine clearance (range) [mL/min]	74.7 (31.6–226.1)	73.6 (32.0–226.1)
No. (%) of patients in each creatinine clearance category		
<30 mL/min	0	0
30–50 mL/min	16 (19.8)	12 (21.8)
50–80 mL/min	27 (33.3)	19 (34.5)
≥80 mL/min	38 (46.9)	24 (43.6)
Type of SSTI		
Deep skin infection	17 (20.7)	11 (20.0)
Wound, burn, and surgical wound	45 (54.9)	32 (58.2)
Erosion and ulcer	18 (22.0)	11 (20.0)
Others	2 (2.4)	1 (1.8)
Median baseline CPK (range) [U/L]	48.5 (10.0–243.0)	50.0 (10.0–243.0)

3.2. Population PK model

The final updated population PK model was a 2-compartment model with first-order elimination, parameterized in terms of CL, central volume of distribution (V1), intercompartmental clearance (Q), and peripheral volume of distribution (V2), with intersubject variability using exponential error models. The following covariates were identified to be statistically significant ($P < 0.001$): body temperature effect on CL, sex effect on CL, effect of the IEAC final diagnosis subgroup on CL, creatinine clearance effect on CL nondialysis, infection status effect on V2, and body weight on Q and V2.

The final parameter estimates (mean [%SEM]) were $CL_{nondialysis}$ = 0.823 (2.3) L/h, $CL_{dialysis}$ = 0.264 (5.1) L/h, Q = 3.07 (4.9) L/h, V1 = 5.29 (2.6) L, and V2 = 3.34 (1.9) L, for subjects with median values of covariates. The final parameter estimates are similar to those from Dvorchik's model, with improved precision. The diagnostic plots showed a good fit of the final population PK model to the observed daptomycin concentrations in plasma (Supplementary Figure 1). The predictive ability of the model was evaluated using the visual predictive check. Fig. 1 shows the observed data and the lines corresponding to the 5th, 50th, and 95th percentiles of the simulated data (n = 1000) for daptomycin. It can be seen that, overall, the final PK model for daptomycin predicts the observed concentrations well. PK parameters in patients who received daptomycin at 4 mg/kg/day are determined based on the empirical Bayesian PK parameter estimates from the final model as shown in Table 3. The GMs of $AUC_{0-24\ h}$ at day 1 and steady state were 260 μg · h/mL (95% CI 243–278) and 359 μg · h/mL (95% CI 327–395), respectively.

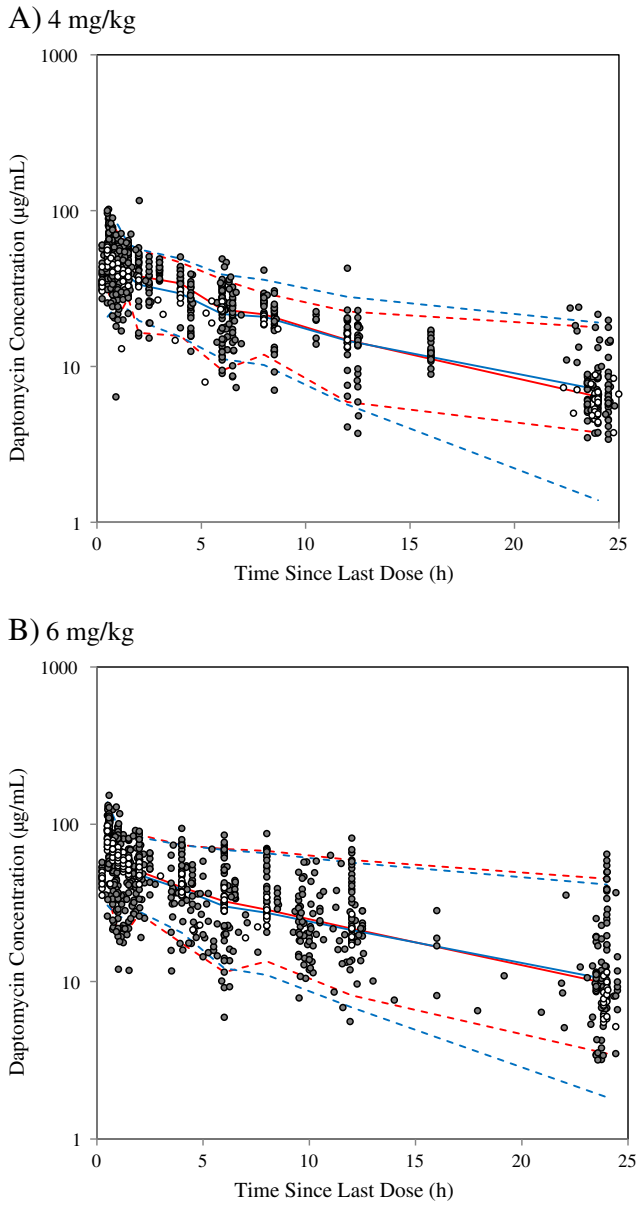

Fig. 1. Visual predictive checks stratified for (A) 4 mg/kg and (B) 6 mg/kg doses at a steady state. The solid red line represents the median observed daptomycin concentrations, and the solid blue line represents the median simulated concentrations. The 5th and 95th percentiles for observed data are presented with dashed red lines, and 5th and 95th percentiles for simulation data are shown as dashed blue lines. The observed daptomycin concentrations are represented by circles (●: non-Japanese, ○: Japanese).

Table 2
Susceptibility of baseline *S. aureus* isolates to daptomycin for patients in the PK/PD analysis population for efficacy.

Organisms	MIC (μg/mL)						Total
	≤0.06	0.12	0.25	0.5	1	2	
MRSA	0	0	13	31	0	0	44
MSSA	0	0	6	4	1	0	11

MSSA = methicillin-sensitive *S. aureus*.
Threshold of "susceptible (S)" category in the CLSI interpretive standards for *S. aureus* is 1 μg/mL.

3.3. PD analysis

The duration of daptomycin treatment in the PK/PD analysis population for efficacy was 10.5 ± 3.2 days (range 5–14 days). The clinical and microbiological response rates were 94.5% (52/55 patients) and 69.1% (38/55 patients), respectively. Clinical and microbiological responses by exposure grouped by quartiles are shown in Table 4. For day 1 $AUC_{0-24\ h}$/MIC, there was no relationship between response and exposure grouped by quartiles (P = 0.825 for clinical success and P = 0.429 for microbiological success). Similarly, no significant relationships were found between day 1 $AUC_{0-24\ h}$ and clinical (P = 0.758) or microbiological response (P = 0.802). On the basis of the logistic regression model with day 1 $AUC_{0-24\ h}$/MIC as a continuous covariate, the odds ratio for 100 units was 1.03 (95% CI 0.73–1.45, P = 0.875) for clinical success and 0.91 (95% CI 0.94–1.09, P = 0.421) for microbiological

Table 3
PK parameters of daptomycin in patients in PK/PD analysis populations for safety and efficacy.

PK parameter	GM (95% CI)	Minimum	Median	Maximum
PK/PD analysis population for safety (n = 82)				
Day 1 $AUC_{0\text{-}24\ h}$ (μg · h/mL)	260 (243, 278)	118	264	592
Steady-state $AUC_{0\text{-}24\ h}$ (μg · h/mL)	350 (322–381)	86	357	769
C_{min} (μg/mL)	5.6 (4.9–6.5)	0.3	6.2	19.5
C_{max} (μg/mL)	42.7 (39.8–45.8)	12.8	45.3	72.1
$t_{1/2}$ (h)	10.8 (10.1–11.5)	4.5	10.7	20.1
V_{ss} (L/kg)	0.177 (0.160–0.181)	0.095	0.165	0.418
CL (mL/h/kg)	11.5 (10.6–12.5)	5.2	11.3	46.8
PK/PD analysis population for efficacy (n = 55)				
Day 1 $AUC_{0\text{-}24\ h}$ (μg · h/mL)	260 (243, 278)	118	265	592
Steady-state $AUC_{0\text{-}24\ h}$ (μg · h/mL)	359 (327–395)	164	359	769
C_{min} (μg/mL)	5.9 (5.0–6.9)	1.2	6.6	19.5
C_{max} (μg/mL)	43.2 (40.0–46.7)	17.8	45.3	72.1
$T_{1/2}$ (h)	11.0 (10.2–11.9)	5.9	10.8	20.1
V_{ss} (L/kg)	0.175 (0.158–0.181)	0.103	0.165	0.418
CL (mL/h/kg)	11.2 (10.2–12.3)	5.2	11.1	24.4

C_{max} = maximum plasma concentration at steady state.

success. Similarly, no significant relationships were found between steady-state $AUC_{0\text{-}24\ h}$ and clinical or microbiological response when evaluated using a logistic regression model (Table 5).

Only 1 patient who met the CPK elevation criteria had a normal CPK level at baseline (135 U/L) and remained normal on day 7 (48 U/L). The CPK level increased to 1610 U/L on day 12 (end of treatment [EOT]), reached 2545 U/L on day 13, and then decreased to normal on day 18 (6 days after the EOT). The C_{min} of this patient was 5.37 μg/mL. Overall, no significant relationship was found between peak CPK values and daptomycin C_{min} (Pearson's correlation coefficient −0.0452). The analyses of the relationship between CPK elevation and C_{min} grouped by quartiles and as a continuous covariate were planned, but these analyses were not performed due to only 1 event of CPK elevation.

4. Discussion

We established a population PK model by adding data from Japanese subjects to the data reported by Dvorchik et al. (2004). The final parameter estimates from our study ($CL_{nondialysis}$ = 0.823 L/h, Q = 3.07 L/h, V1 = 5.29 L, V2 = 3.34 L for subjects with median values of covariates) were similar to those from the previous model (median [percent relative standard error]; $CL_{nondialysis}$ = 0.807 [2.9] L/h, Q = 3.46 [6.3] L/h, V1 = 4.80 [4.2] L, V2 = 3.13 [2.7] L) (Dvorchik et al., 2004). This model successfully fit the daptomycin concentration–time data in Japanese, allowing an estimation of daptomycin PK parameters and characterization of the covariates affecting the PK properties of daptomycin.

In our study of patients with SSTIs who received daptomycin at 4 mg/kg/day, GM steady-state $AUC_{0\text{-}24\ h}$ was 359 (min-max 359–1,769 μg · h/mL). Similarly, Dvorchik et al. (2004) reported that the median $AUC_{0\text{-}\infty}$ was 339 (min-max 161–1144) μg · h/mL in patients with gram-positive bacterial infection. In contrast, in a study of healthy subjects, Dvorchik et al. (2003) reported an $AUC_{0\text{-}24\ h}$ for daptomycin of 494 ± 75 μg · h/mL at day 7, and Hasegawa et al. (2011) reported that mean $AUC_{0\text{-}24\ h}$ was 424.7 (95% CI 392.1–460.1) μg · h/mL at day 7. Based on these results, the $AUC_{0\text{-}24\ h}$ in patients with infection tended to be lower than that in healthy subjects. The C_{min} in our study (5.8 μg/mL) was almost identical to the value (5.6 ± 0.8 μg/mL) reported by Hasegawa et al. (2011).

The small number of patients (n = 3) with clinical failure made it difficult to identify relationships between clinical efficacy and PK/PD indices. Irrespective of looking at the data with AUC or AUC/MIC ratio evaluated continuously or categorically, there was no evidence of PK-

Table 5
Evaluation of the relationships between PK/PD indices and clinical or microbiological responses to daptomycin based on a logistic regression model with a covariate for PK/PD index.

PK/PD indices	Clinical response		Microbiological response	
	Odds ratio (95% CI) for 100 units	*P* value	Odds ratio (95% CI) for 100 units	*P* value
Steady state				
$AUC_{0\text{-}24\ h}$ (μg · h/mL)	1.09 (0.44–2.68)	0.852	0.77 (0.51–1.17)	0.217
$AUC_{0\text{-}24\ h}$/MIC	1.02 (0.82–1.27)	0.872	0.91 (0.82–1.01)	0.071
Day 1				
$AUC_{0\text{-}24\ h}$ (μg · h/mL)	1.19 (0.32–4.50)	0.793	1.01 (0.55–1.86)	0.972
$AUC_{0\text{-}24\ h}$/MIC	1.03 (0.73–1.45)	0.875	0.94 (0.81–1.09)	0.421

The odds ratios are based on the odds of a successful response for both clinical and microbiological endpoints.

Table 4
Clinical and microbiological responses by grouped exposure or PK/PD indices (n = 55).

Exposure or PK/PD index	Quartile group		Clinical response		Microbiological response	
			Success/n (%)	*P* value	Success/n (%)	*P* value
Steady state						
$AUC_{0\text{-}24\ h}$ (μg · h/mL)	1	164 to <289	12/13 (92.3)	0.758	9/13 (69.2)	0.596
	2	289 to <359	13/14 (92.9)		10/14 (71.4)	
	3	359 to <433	14/14 (100.0)		11/14 (78.6)	
	4	433–769	13/14 (92.9)		8/14 (57.1)	
$AUC_{0\text{-}24\ h}$/MIC	1	289 to <650	12/13 (92.3)	0.825	11/13 (84.6)	0.116
	2	650 to <856	14/14 (100.0)		10/14 (71.4)	
	3	856 to <1240	13/14 (92.9)		9/14 (64.3)	
	4	1240–3076	13/14 (92.9)		8/14 (57.1)	
Day 1						
$AUC_{0\text{-}24\ h}$ (μg · h/mL)	1	118 to <201	12/13 (92.3)	0.758	7/13 (53.8)	0.802
	2	201 to <265	13/14 (92.9)		13/14 (92.9)	
	3	265 to <342	14/14 (100.0)		8/14 (57.1)	
	4	342–592	13/14 (92.9)		10/14 (71.4)	
$AUC_{0\text{-}24\ h}$/MIC	1	147 to <484	12/13 (92.3)	0.825	10/13 (76.9)	0.429
	2	484 to <625	14/14 (100.0)		11/14 (78.6)	
	3	625 to <848	13/14 (92.9)		7/14 (50.0)	
	4	848–2156	13/14 (92.9)		10/14 (71.4)	

The groups of steady-state $AUC_{0\text{-}24\ h}$ or steady-state $AUC_{0\text{-}24\ h}$/MIC were divided by quartiles: group 1, minimum to <25th percentile; group 2, 25th percentile to greater than median; group 3, median to <75th percentile; group 4, 75th percentile to maximum.

PD relationships for efficacy even in the analyses of microbiological response for which there was a higher percentage of failures. Narrow exposure ranges and/or a narrow MIC range may impede the identification of PK-PD relationships for efficacy. In addition, the diversity of SSTIs (cellulitis, abscess, wound, surgical wound, burn, ulcer, and decubitus) and the involvement of surgical drainage/debridement may complicate the analysis of clinical response. For the analysis in SSTIs, semiquantitative microbiological assessment and/or assessment of efficacy earlier in therapy may be more suitable to find the cut-off value for efficacy (Food and Drug Administration, 2013).

Using the definition of Bhavnani et al. (2010), only 1 patient (with a peak CPK of 2545 U/L) met the criteria for CPK elevation during treatment with daptomycin at 4 mg/kg/day. The C_{min} of this patient was 5.37 μg/mL. Conversely, among 108 patients treated with daptomycin at 6 mg/kg/day for *S. aureus* bacteremia, Bhavnani et al. (2010) found 6 patients who matched their definition of CPK elevation, and they reported significant relationships between C_{min} and AUC and the probability of CPK elevation. Using classification and regression tree analysis, they reported C_{min} ≥24.3 μg/mL as the threshold associated with increased probability of CPK elevation. We also evaluated CPK elevation according to the definition of the US labeling recommendation for the discontinuation of daptomycin treatment: 1) patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation to a level >1000 U/L (approximately 5 × ULN) or 2) patients without reported symptoms who have marked elevation of CPK to a level of >2000 U/L (approximately 10 × ULN). However, only the same single patient met these criteria.

To analyze the relationship between CPK elevation and C_{min} in patients treated with daptomycin at 4 mg/kg/day, we conducted analysis using peak CPK during treatment as a serial variable. No significant relationship between peak CPK and C_{min} was found in patients receiving daptomycin at 4 mg/kg/day (Pearson's correlation coefficient −0.0452). The main reason for the lack of correlation is considered to be the lower exposure level. In addition to this, relatively shorter therapy and twice a week measurement of CPK may cause lack of relationship. The occurrence of CPK elevation was demonstrated in the first 2 weeks in almost all patients (Bhavnani et al., 2010). CPK was evaluated 3 times per week in the study by Bhavnani et al. (2010). In our study, C_{min} values ranged from 1.2 to 19.5 μg/mL and did not reach the threshold of 24.3 μg/mL reported by Bhavnani et al. (2010).

The incidence of CPK elevation due to daptomycin (4 mg/kg every 24 h) has been reported in comparison with conventional antibiotics (cloxacillin, flucloxacillin, nafcillin, oxacillin, or vancomycin) in 2 randomized, international trials involving patients with complicated skin and skin structure infections (Arbeit et al., 2004), and there was no significant difference between the treatment groups (2.8% versus 1.8%, $P = 0.26$). Considering the low incidence rates together with the low C_{min} level that we described in this report, monitoring the C_{min} of daptomycin to investigate the potential risk of CPK elevation in patients receiving 4 mg/kg/day for the treatment of SSTIs does not appear to be warranted. These findings should, however, not discourage routine CPK monitoring during daptomycin therapy.

Our analyses have some limitations. A limited number of failures together with a limited exposure range as shown in Table 3 hindered the ability to identify PK/PD relationships for efficacy. In addition, the MIC range was limited, and the power was an issue due to limited sample size for these analyses. In conclusion, based on the results of these analyses, daptomycin exposure in patients with SSTIs treated with daptomycin at 4 mg/kg/day was not associated with clinical or microbiological outcome. Additionally, the dosage administered did not reach the critical level associated with CPK elevation. Future PK/PD analyses based on data from patients with MRSA infections receiving daptomycin over a wider dose range will be useful to better understand the nature of such relationships.

Conflict of interest and source of funding

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References

Aikawa N, Kusachi S, Mikamo H, Takesue Y, Watabnabe S, Tanaka Y, et al. Efficacy and safety of intravenous daptomycin in Japanese patients with skin and soft tissue infections. J Infect Chemother 2013;19:447–55.

Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis 2004;38:1673–81.

Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin Infect Dis 2010;50:1568–74.

Dvorchik BH, Brazier D, DeBruin MF, Arbeit RD. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. Antimicrob Agents Chemother 2003;47:1318–23.

Dvorchik B, Arbeit RD, Chung J, Liu S, Knebel W, Kastrissios H. Population pharmacokinetics of daptomycin. Antimicrob Agents Chemother 2004;48:2799–807.

Food and Drug Administration. Acute bacterial skin and skin structure infections: developing drugs for treatment. Guidance for Industry 2013; 2013 [http://www.fda.gov/downloads/Drugs/Guidances/ucm071185.pdf].

Hasegawa S, Miki M, Wan K, Aoki I. A phase I study in Japanese healthy subjects with single and multiple intravenous dose of daptomycin (MK-3009). Antibiot Chemother 2011;27:135–48.

Louie A, Kaw P, Liu W, Jumbe N, Miller MH, Drusano GL. Pharmacodynamics of daptomycin in a murine thigh model of *Staphylococcus aureus* infection. Antimicrob Agents Chemother 2001;45:845–51.

Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. Antimicrob Agents Chemother 2004;48:63–8.